



Chemicals for the Information Age

## ESCO Company Limited Partnership

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December 5, 2003



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201-14878

Mike Leavitt, Administrator  
U.S. Environmental Protection Agency  
P.O. Box 1473  
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

RE: EPA HPV Registration No.:

Dear Administrator Leavitt,

ESCO Company Limited Partnership is electronically submitting the enclosed revised test plan and revised robust summaries for the HPV Challenge Program, AR-201. The revised test plan and revised robust summaries are being submitted for the chemical category designated as the "keto acid" category. This keto acid category includes the following two chemicals:

Benzoic acid, 2-[4-(diethylamino)-2-hydroxybenzoyl], (C.A.S. No. 5809-23-4), and

Benzoic acid, 2-[4-(dibutylamino)-2-hydroxybenzoyl], (C.A.S. No. 54574-82-2).

This electronic submission includes this cover letter in Adobe Acrobat format (file name: Cover Letter for Keto Acid Submission-Revised.pdf), the revised keto acid robust summaries in Adobe Acrobat format (file name: Keto Acid Category Robust Summaries-Revised.pdf), and the revised keto acid test plan in Adobe Acrobat format (file name: Keto Acid Category Test Plan-Revised.pdf). Please post these revised submissions on the EPA HPV Challenge web site.

Included below is a summary of the comments that were received from the EPA on our test plan and robust summaries and our response to those comments.

### Test Plan

#### General

**Comment:** In the test Plan Conclusion on page 8, the submitter mentioned that keto acids are used as "closed system intermediates." However, the test plan does not include a formal claim of closed system intermediate status. The submitter may wish to clarify this statement.

**Response:** The test plan was revised to remove the references to a closed system intermediate to avoid confusion with the formal claim of a closed system intermediate.

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December 5, 2003

Comment: The submitter needs to correct the typographical errors in tables in the test plan (on pages 1 and 2) and robust summaries (on page 1). The field "Color Former Name" should be replaced with "Keto Acid Name."

**Response: The test plan and the robust summaries were revised to correct these typographical errors.**

#### Physicochemical Properties

Comment: *Boiling point.* In the robust summary, the submitter only indicates that these chemicals melt at temperatures above 201 °C, and that no boiling point data have been generated. The submitter needs to provide quantitative boiling point data for these chemicals. The high melting points suggest that these chemicals boil or decompose at very high temperatures. OECD guidelines indicate that estimated values are accepted for chemicals whose estimated boiling point exceeds 300 °C.

**Response: The test plan and robust summaries have been revised to include estimated boiling point data for each of the keto acids in the category.**

Comment: *Vapor pressure.* The submitter provided a vapor pressure of 13 Pa (0.098 mm Hg) at 20 °C for BuKeto acid in the robust summaries. The submitter proposed a read-across approach for EtKeto acid. EPA found estimated vapor pressures of  $1.76 \times 10^{-10}$  and  $1.47 \times 10^{-11}$  mm Hg at 25 °C for EtKeto and BuKeto acid, respectively (using MPBPWIN v 1.40, melting points of 201 and 187 °C were entered into MPBPWIN for the ethyl and butyl derivatives respectively). There is a large discrepancy between the estimated vapor pressure obtained by EPA and the measured vapor pressure provided by the submitter. While the structures of the two category members are very similar, and it would be expected that they would have similar vapor pressures, this discrepancy indicates that there may be an error in the submitter's data for the BuKeto acid. Therefore, using the vapor pressure for BuKeto acid to satisfy the EtKeto acid endpoint may not be appropriate. The submitter needs to verify the value provided. According to OECD guidelines, calculations showing a value  $<1 \times 10^{-5}$  Pa ( $7.5 \times 10^{-8}$  mm Hg) at 25 °C may be acceptable in lieu of measuring vapor pressure.

**Response: The vapor pressure provided for Buketo acid was from a toxicokinetic assessment that reviewed data from other studies. The vapor pressure was listed in the assessment under physicochemical properties, but there is not a vapor pressure study available that verifies this result. The robust summary and the test plan were revised to remove the value from the toxicokinetic assessment and include the estimated values based on the EPA model MPBPWIN v1.40.**

Comment: *Partition Coefficient.* The submitter needs to provide detailed information on the method used and clearly indicate how the value for EtKeto acid will be related to that of BuKeto acid.

December 5, 2003

**Response: The robust summary and test plan were revised to provide more information about the method used and indicate how the value for EtKeto will be related to that of BuKeto acid. The test plan and robust summary were also revised to include an estimated value of the partition coefficient for EtKeto acid.**

Comment: *Water solubility*. The submitter needs to state clearly how the water solubility from EtKeto acid will be related to that of Buketo acid.

**Response: The robust summary and test plan were revised to include estimated qualitative values for water solubility for EtKeto acid which more clearly shows how the water solubility is related to the measured water solubility values of Buketo acid.**

#### Environmental Fate

Comment: *Stability in water*. The test plan states, "The photodegradation and hydrolysis endpoints for the keto acids were estimated with the EPA model, EPIWin... Very little of the keto acids dissolve in water, so hydrolysis is... not a very likely route of degradation." Hydrolysis of these chemicals is unlikely because the molecules contain no hydrolyzable functions. The test plan and robust summary should be revised to reflect this (a code of "NA" rather than "A" should appear in Table 1 of the test plan).

**Response: The test plan was revised to include the code of "NA" in Table 1 instead of "A." The test plan and robust summaries were revised to include the statement that hydrolysis of these chemicals is unlikely because the molecules contain no hydrolyzable functions.**

Comment: *Biodegradation*. The submitter's code of "C" rather than "A" should appear in Table 1 of the test plan.

**Response: The test plan was revised to include the code of "C" for EtKeto acid in Table 1 regarding biodegradation instead of the code "A."**

Comment: *Fugacity*. The submitter needs to include the model input values in the robust summary for fugacity.

**Response: The robust summary was revised to include the input values for the fugacity model.**

#### Health Effects

Comment: *Developmental toxicity*. The submitter needs to provide a separate robust summary describing developmental effects from the one-generation toxicity study on BuKeto acid.

**Response: The robust summary was revised to include a separate developmental toxicity robust summary for the one-generation toxicity study on BuKeto acid.**

December 5, 2003

### Specific Comments on the Robust Summaries

#### Generic comments

Comment: The submitter needs to state the purity of the test substance in all robust summaries.

**Response: The robust summaries were revised to state the purity of the test substance.**

#### Health Effects

Comment: *Acute Toxicity*. Information missing from the robust summary of the acute oral toxicity study in rats exposed by gavage to EtKeto acid includes the dosing volume, the clinical signs observed and body weight effects (if measured).

**Response: The robust summary of the acute oral toxicity study for EtKeto was revised to include the dosing volume, the clinical signs observed, and body weight effects.**

Comment: *Genetic toxicity*. Robust summaries for bacterial mutagenesis assay and an *in vitro* chromosomal aberration assay on BuKeto acid did not provide information on the number of replicates and number of metaphases examined.

**Response: The robust summaries for the bacterial mutagenesis assay and an *in vitro* chromosomal aberration assay on BuKeto acid were revised to include the number of replicates and the number of metaphases examined.**

#### Ecological Effects

Comment: *Fish*. Details missing include an adequate description of the test substance, water quality parameters (e.g., pH, temperature, dissolved oxygen), guideline used, and assigned reliability code.

**Response: The robust summaries for the fish studies were revised to include an adequate description of the test substance, water quality parameters, and the OECD guideline used.**

Comment: *Invertebrates*. Details missing include an adequate description of the test substance, dose-response information, water quality parameters (e.g., pH, temperature, dissolved oxygen), guideline used, and an assigned reliability code.

**Response: The robust summaries for the invertebrate studies were revised to include an adequate description of the test substance, dose-response information, water quality parameters, and the OECD guideline used.**

Comment: *Algae*. Details missing include study type (e.g. static, semi-static, flow-through), an adequate description of the test substance, dose-response information, and water quality parameters (e.g., pH, temperature).

December 5, 2003

**Response: The robust summary for the algae study was revised to include the study type, an adequate description of the test substance, dose-response information, and water quality parameters.**

Included below is a summary of the comments that were received from Environmental Defense on our test plan and robust summaries and our response to those comments.

#### Test Plan

Comment: No common names or synonyms are listed for these chemicals. If there are none, that should be stated.

**Response: The chemicals in the keto acid category are commonly referred to as EtKeto Acid and BuKeto Acid.**

Comment: Section 4.4 Ecotoxicity. It is stated that BuKeto Acid is mildly toxic to fish and mildly inhibitory to algal growth. However, the data presented indicate that it is more than mildly toxic. It also has significant toxicity to aquatic invertebrates, as shown in Table 4. Further, given the low solubility of BuKeto and its failure to biodegrade, as shown in Table 3. It could well be that a significant hazard would be posed by release of either Keto Acid into a large body of water where more of it would be solubilized and could have a more widespread effect. We note that both PCBs and many halogenated insecticides are less soluble than these chemicals.

**Response: The test plan was revised to remove the language that characterized the toxicity of the chemicals. Both EtKeto acid and BuKeto acid are used as chemical intermediates in making color formers. These intermediates are transported in supersacks by truck and in supersacks in containers by ships and are not likely to be released into bodies of water. Also, because these chemicals are not very soluble in water, they could probably be recovered from a spill into water. These chemicals are used by other chemical facilities to manufacture color formers; they are not intended to be stored or used in the environment like PCBs or halogenated insecticides.**

Comment: Sections 4.5 & 5, Toxicology & Test Plan Conclusion. The test plan claims that "The data provided for acute oral toxicity are consistent for the keto acids" and "The keto acids in this category show a clear pattern of low toxicological concern, so no further toxicological testing is planned for the keto acid category" are considerable overstatements. The only such data available for EtKeto Acid are from a single acute toxicity study test obtained with a single dose. Further, the single high dose was dissolved in corn oil and, as noted on page 59 of the Robust Summary, was probably not absorbed from the gastrointestinal tract. These conclusions do not appear to be sufficiently supported in light of the fact that only one keto acid has been adequately tested. We defer to the EPA to determine the need for additional studies of EtKeto Acid.

**Response: The test plan was revised to remove the statements characterizing the toxicity of the keto acids.**

Comment: Section 5, Test Plan Conclusion. The sponsor states that it uses both of these chemicals as closed system intermediates. The Test Plan does not, however, provide sufficient information, as specified in EPA's guidance, to establish this status. Nor does it provide any information regarding the production and use of these chemicals by other companies, the potential for occupational exposure, or other uses that might result in human and/or environmental exposure.

**Response: The test plan was revised to remove the reference regarding closed system intermediates. Both EtKeto acid and BuKeto acid are used as chemical intermediates in making color formers. These intermediates are transported in supersacks by truck and in supersacks in containers by ships.**

Comment: It is noted that there is a very significant difference in the "Nominal Concentrations" and the "Measured Concentrations" of BuKeto Acid in many of the aquatic toxicity studies. In some cases these differences are as great as ten-fold. What is the sponsor's explanation for this? Is it a reflection of differences in the quality of the data?

**Response: The difference in the "Nominal Concentrations" and the "Measured Concentrations" in many aquatic toxicity studies can be explained by the low water solubility of the keto acids.**

Included below is a summary of the comments that were received from Physicians Committee for Responsible Medicine (PCRM) on our test plan and robust summaries and our response to those comments.

Comment: PCRM is concerned that no further animal testing be conducted.

**Response: ESCO Company does not anticipate that any further animal testing would be necessary.**

If you have any questions, please call me at 231-727-6459 or my e-mail address is [Bkatje@escocompany.com](mailto:Bkatje@escocompany.com).

Sincerely,

Bruce Katje  
Regulatory Compliance Manager

Attachments